Future Therapies for Exudative AMD

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Financial Disclosure

• Consultant/Advisor: Alcon, Allergan, Bausch&Lomb, Regeneron, Genentech, Neurotech, GSK, Santeen, Pfizer, Allegro

Angiogenesis in AMD is a Complex Cascade of events


Current Paradigm – Block VEGF

**Subjects Losing <15 Letters From Baseline**

- **MARINA at month 24**
  - Sham (n=238)
  - Ranibizumab 0.5 mg (n=240)

- **ANCHOR at month 24**
  - PDT (n=143)
  - Ranibizumab 0.5 mg (n=139)

*Month 12 was the primary endpoint in both trials; month 24 was a secondary endpoint.

†P<0.01 vs sham; ‡P<0.01 vs PDT.

**Vision Loss/Vision Recovery Limitations in Anti-VEGF Treatment**
- Fibrovascular Proliferation
- RPE Atrophy
- Retinal Damage
- Anti-VEGF Non-Responders
New Therapeutic Trials

- **Fusion protein of key extracellular domains from human VEGF receptors 1 and 2 combined with human IgG Fc**
- **All human amino acid sequence**
- **Binds VEGF tighter than native receptors, bevacizumab, or ranibizumab**
- **Blocks all VEGF-A isoforms and placental growth factor (PlGF)**
- **Increased dimerization efficiency**
- **Lower isoelectric point (PI) than VEGF Trap-Eye which prolongs clearance time**

**Mean Change in Visual Acuity**

- **KH902**
  - Phase III clinical trial completed in naïve patient population in China
Anti-VEGF Gene Therapy for AMD

Cells within the patient's eye direct production of the therapeutic protein

The sFlt01 protein binds VEGF and PlGF

The duration of the AAV2 sFlt01 effect is at least 12 months

Phase I Gene Therapy

- Dose escalation
- Single intravitreal injection
- Duration up to 1 year
- Multi-center
Encapsulated Cell Technology
Neurotech

• Device contains human RPE cells (ARPE-19) genetically modified to secrete a drug
• The device is surgically implanted in the vitreous through a tiny scleral incision and is anchored by a single suture through a titanium loop at one end of the device
• The semi-permeable membrane allows the outward diffusion of drug and other cellular metabolites
• Allows inward diffusion of nutrients necessary to support the cell survival in the vitreous cavity while protecting the contents from host cellular immunologic attack
• “Immunologically privileged”
• Biologic activity demonstrated in CNTF trial

Patient A2301 – 76 Y/O Woman
Gen 2 Double Implant

+25 letter vision gain and ~350µ decrease in central foveal thickness

Baseline
40 Letters 639 um

1 Month
46 Letters 355 um

2 Months
50 Letters 295 um

3 Months
53 Letters 301 um

4 Months
54 Letters 324 um

5 Months
52 Letters 314 um

Encapsulated Cell Technology
Neurotech

• Neurotech device (NT-503) encapsulating VEGF receptor Fc-fusion protein (VEGFR-Fc)–releasing cells.
• This VEGFR-Fc is 20-fold more efficient in neutralizing VEGF compared with ranibizumab NT-503 is confirmed to release VEGFR-Fc constantly up to 1 year in the rabbit vitreous.
• A phase 1 clinical trial of NT-503 for neovascular AMD is ongoing outside of the United States.
P529 Signaling Pathway Inhibition

• Oxygen-induced retinopathy (diabetic retinopathy) model
  – Unlike anti-VEGF antibody, P529 inhibits aberrant vascularization (lower right, upper left)
  – Unlike anti-VEGF, P529 allows normal angiogenesis (central area remains vascularized)
  – Synergizes with anti-VEGF
  – May provide greater safety than anti-VEGF as it does not abrogate "normal" VEGF activity
**P529 Phase I Study**

- A Phase I Open-Label Study to Investigate the Safety, Tolerability and Pharmacokinetic Profile of Single Intravitreal and Subconjunctival Doses of Palomid 529 in Patients with Advanced Neovascular Age-Related Macular Degeneration

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**Integrins**

- **Family of transmembrane heterodimeric proteins**
- Mediate adhesion to the extracellular matrix and between cells
- Direct roles in signaling and modulation of downstream kinase signaling pathways
- Involved in EC migration and prevents EC apoptosis

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**αβ1 Integrin Key Features**

- Adhesion molecule
- Blockade can lead to vessel regression
- “Turned on” in disease
- Up-regulated on several cell types involved in pathological neovascularization

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**Upstream**

- Extracellular Space

**Downstream**

- Developmental angiogenesis
- Angiogenesis: Migration, Proliferation, Vascular permeability

**Integrin Antagonists**

- **Integrins**
  - Family of transmembrane heterodimeric proteins
  - Mediate adhesion to the extracellular matrix and between cells
  - Direct roles in signaling and modulation of downstream kinase signaling pathways
  - Involved in EC migration and prevents EC apoptosis

**Receptor Blockers**

- Fibronectin, Endothelial cell
Volociximab

- Volociximab is a chimeric (82% human/18% murine) IgG4 monoclonal antibody (Mab) against α5β1 integrin

Inhibition of CNV: FA Leakage

Tyrosine kinases are enzymes that provide a central switch mechanism in signal transduction pathways

- Phosphorylation of proteins
- Involved in cell proliferation, metabolism, survival and apoptosis
X-82 is a potential new treatment for wet AMD
It is unique because:
- It is given orally
- It blocks both VEGF and PDGF
This study is designed to evaluate its safety and preliminary efficacy in patients with wet AMD
Completing a Phase 1/2 trial
Orally administered

X-82 for wet AMD
X-82 is able to inhibit pVEGFR, pPDGFR, HUVEC cell growth, and blood vessel tube formation at very low concentrations (~50nM), much lower than what is required for cancer.
X-82 at 50mg is able to reach and exceed the concentration required for anti-angiogenesis
Average AUC of cancer pts 4,6,9 (~572 ng.hr/ml) is 4.5x that of pts taking 50mg QD (1282 ng.hr/ml)
QOD will evaluate if constant inhibition is necessary for efficacy

Effect of X-82 on HUVEC tube formation induced by VEGF

Oncology Patient with AMD
Started X-82 100 mg tablet on 10-25-12
AMD Diagnosed 11-06-12
Symptoms noted at baseline
Official diagnosis: Peripapillary atrophy with peripapillary choroidal neovascular membrane and subretinal blood
BCVA improved from 20/60 to 20/25
Leakage from peripapillary subretinal neovascular membrane has improved
Subretinal fluid is much less
**Pazopanib**

- **Topical tyrosine kinase inhibitor**
- Inhibits multiple targets
  - VEGFR
  - PDGFR
  - c-kit
- **Phase II study - 70 patients – Topical administration**
  - Mean 4.3 letter increase in Va
  - Patients with the CFH TT genotype (the naturally occurring wild type gene) exhibited the **best visual and anatomic response**

**Beyond the VEGF Cascade**

- **VEGF**
  - Vascular Endothelial Growth Factor
- Endothelial cell activation
- Endothelial cell proliferation, migration
- Basement membrane degradation
- Tube formation + remodeling
**PDGF inhibition**

- Platelet derived growth factor (PDGF) regulates cell growth and division
- Block PDGF-B to prevent pericyte recruitment to neovascular vessels - destabilize and shrink CNV.
- E-10030
  - Pegylated aptamer containing 32 monomeric units (32-mer) against PDGF-B

**Combination Therapy**

Does not strip pericytes from mature limbal vessels

**Phase I: Combination Rx**

Mean VA Change from Baseline Visual Acuity (ETDRS Letters)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Letters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td></td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Week 4</td>
<td>11.2</td>
<td>12.3</td>
<td>14.0</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td></td>
<td></td>
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<tr>
<td>Week 12</td>
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**Phase 1: Combination Treatment**

Mean Change from Baseline Central Foveal Thickness

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
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</thead>
<tbody>
<tr>
<td><strong>Microns</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>387</td>
<td>380</td>
<td>245</td>
<td>230</td>
</tr>
<tr>
<td>Week 4</td>
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<td>Week 8</td>
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<td>Week 12</td>
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</tbody>
</table>
**Phase I: Combination Rx**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Post-combination therapy 1 month</th>
<th>Post-combination therapy 2 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/80</td>
<td>20/32 +21 Letters</td>
<td>20/25 +27 Letters</td>
</tr>
<tr>
<td>706 microns</td>
<td>264 microns</td>
<td>238 microns (-468 microns)</td>
</tr>
</tbody>
</table>

**Role of Microtubules: Shape**

- Microtubules are essential to maintain cell’s elongated shape (cytoskeleton)
- As the cell matures, the shape is maintained by actin

**Combretastatin A4 phosphate**

- Tubulin-binding agent destroys the internal skeleton of immature endothelial cells changing the shape from flat to round, plugging the vessels
- Reduces blood flow in neovascular vessels

**Combretastatin A-4-Phosphate Study with Neovascular AMD**
**Combretastatin A4 phosphate**

- Phase II study completed
- Targeting patients with Polypoidal Choroidal Vasculopathy

**OC-10X**

- Lipid soluble quinazolinone
- Inhibits tubulin in neovascular vessels
- Administered **topically** with good target concentrations in the back of the eye
- Significant *antiangiogenic* and *angiolytic* activity in laser induced mouse CNV model

**Squalamine**

- Small molecule aminosterol
- Novel intracellular, anti-angiogenic mechanism of action
- Potent at low nano-molar tissue concentrations
- Inhibitor of VEGF, PDGF, and bFGF signaling through chaperoning of the modulatory protein Calmodulin

**Previous Intravenous Clinical Program**

- Studied in over 450 patients using an intravenous formulation
  - 250+ patients with Wet-AMD
  - 200+ oncology patients (solid tumors, ovarian, lung, and prostate)
  - Safely tested in wet-AMD at doses of up to 160mg per infusion

- Clinical Data in wet-AMD trials
  - Demonstrated biologic effect
  - Some gains in visual acuity
  - Strong maintenance of vision
  - Effect in advanced, low vision wet-AMD
Squalamine Previous Intravenous Clinical Program

- Entered phase III trials for wet-AMD under fast track status and a Special Protocol Assessment (US FDA)
  - Discontinued due to
    - Enrollment difficulty of an IV approach
    - Changing competitive landscape of ranibizumab and bevacizumab Lack of commercial potential for chronic IV infusions
    - Suboptimal dosing due to relatively short half life when given systemically

Squalamine New Topical Clinical Program

- Preclinical testing
  - Safe to ocular tissues
  - Anti-angiogenic concentrations achieved in posterior sclera and choroid
  - No quantifiable uptake in aqueous humor
  - Negligible systemic uptake
- Clinical Trials
  - Phase II multi-center, randomized, placebo controlled trial
  - Treatment of wet-AMD
  - Initiation expected in mid 2012

hl-con1

- hl-con1 is a recombinant protein designed to target Tissue Factor (TF)
  - hl-con1 binds very tightly to TF
  - TF present on inner surface of CNV but not normal blood vessels
  - Binding of hl-con1 to CNV triggers cell-mediated cytotoxicity via Natural Killer cells
  - Anticipated result: REGRESSION of CNV

Pig wet AMD Model: hl-con1 Triggers CNV Regression in a Dose-Dependent Manner

- hl-con1 destroys established laser-induced CNV in a dose-dependent fashion
**Phase 1 Trial: hI-con1 for Exudative AMD**

- **Phase I:** Open-label, dose escalation study
- **Objective:** Evaluate the safety and tolerability of hI-con1™
- **Study parameters:**
  - 18 subjects (6 per dose level)
  - Dose scheme: 3 dose levels of hI-con1™ (60 mg, 150 mg and 300 mg)
  - 24 weeks follow up
- During Phase 1, the 4th, 5th, and 6th subjects enrolled in each cohort must have total lesion area < 6 DA (total area of detachment) (15.24 mm²), of which at least 50% must be actively leaking, and 30% should be classic on the angiography, and no more than 3 prior injections of any therapy for the treatment of CNV

**Phase 1 Trial: Preliminary Results**

- Safe at all doses tested
- No safety concerns in patients who received anti-VEGF after two weeks of hI-con1
- Signal of biologic activity seen
- Regression of CNV and reduction in OCT leakage in some cases
- Dose response noted
- Effects seen in some anti-VEGF® partial responders
- Full data presentation at ARVO

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**Bioactive Lipids**

- Bioactive lipids may play a role in ocular angiogenesis, in particular Sphingosine-1-phosphate (S1P)
- **S1P has an effect on angiogenesis, fibrosis, pericyte ensheathment and macrophage recruitment**
- Anti-S1P therapy potential target for the treatment of exudative AMD - Sphingomab
- Phase I trial: reduction in CNV activity
**DARPin MP0112**

**Designed Ankyrin Repeat Protein**

**DARPin Target**

- Novel class of binding proteins
- High affinity and specificity for many targets
  - MP0112
- VEGF antagonizing DARPin
  - IC50 of <10 pM
- Half-life in the eye >6 days
- Stable at RT for >several months
- Produced at 7-8 g/L in bacteria (E Coli)
- Formulation as a liquid
- Well tolerated in phase 1 testing

**In vitro VEGF Inhibition Assay**

**MP0112: Possible less frequent dosing**

A. PK and stability
   - Half life: MP0112 >6 days
   - Half-life: Ranibizumab = 3 days
   - Stability: MP0112 >>> Ranibizumab

B. Efficacy
   - IC50: MP0112 <10 pM
   - IC50: Ranibizumab >250 pM

**Drug activity in the vitreous over time**

**Complement inhibition**

- Complement protein polymorphisms are associated with drusen formation and all stages of AMD
- Complement inhibition could provide therapeutic benefits at various stages of disease progression
  - Choroidal neovascularization
  - Transition from dry to wet AMD
  - Geographic atrophy
  - Drusen formation

**X-Ray Therapy**

- X-Ray beams
- Robotic control with eye stabilization
- Non-invasive
- Outpatient

*Oraya Therapeutics*
**Other Approaches**

- Steroids
  - Dexamethasone
- Vitreolytics
  - AL-78898
- Radiation
  - Internal – Surgical Delivery
  - External – Office Based Delivery

**Sustained Drug Delivery**

- Sustained Release Implant
  - Surgically implanted – Retisert, Flucinolone Implant
- External – Replenish device
- Encapsulated Cell Technology
  - Miniature drug “factory” - producing drug in implanted device
- Adenoviral Vector
  - Viral gene delivery to cells resulting in production of desired drug/agent

**Sustained Drug Delivery**

- Iontophoresis
  - External anterior delivery of drug using electrical charge
- Microparticles/Nanoparticles
  - Small slow release particles containing active drug
- Phase Transition Gel
  - Liquid formulation on injection change to sustained release gel in vitreous

**Summary: Current and Future Therapeutics**

- Pegaptanib
- Ranibizumab
- Bevacizumab
- VEGF-Trap
- KH902
- MP9112
- AAV2 sFlt01
- Sirolimus
- Everolimus
- P529
- RTP801
- AAV2 sFlt01
- Integri - Valscolimus
- RTki - Pazopanib
- Sphingol
- Complement Inhibitors
- Steroids
- Vitreolytics
- Radiation
- Cobretastatin
- Oc-10X
- Tirol - Pazopanib
Thank You